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REVIEW

Effectiveness, safety and efficacy of INTELLiVENT–adaptive support ventilation, a closed–loop ventilation mode for use in ICU patients – a systematic review

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ABSTRACT

Introduction: INTELLiVENT–Adaptive Support Ventilation (INTELLiVENT–ASV), an advanced closed–loop ventilation mode for use in intensive care unit (ICU) patients, is equipped with algorithms that automatically adjust settings on the basis of physiologic signals and patient's activity. Here we describe its effectiveness, safety, and efficacy in various types of ICU patients.

Areas covered: A systematic search conducted in MEDLINE, EMBASE, the Cochrane Central register of Controlled Trials (CENTRAL), and in Google Scholar identified 10 randomized clinical trials.

Expert opinion: Studies suggest INTELLiVENT–ASV to be an effective automated mode with regard to the titrations of tidal volume, airway pressure, and oxygen. INTELLiVENT–ASV is as safe as conventional modes. However, thus far studies have not shown INTELLiVENT–ASV to be superior to conventional modes with regard to duration of ventilation and other patient–centered outcomes. Future studies are needed to test its efficacy.

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Artificial ventilation; automated ventilation; closed–loop ventilation; effectiveness; efficacy; intensive care unit; INTELLiVENT–ASV; invasive ventilation; protective ventilation; safety

1. Introduction

Mechanical ventilation is an often needed and at times even life–saving intervention in intensive care unit (ICU) patients. Since its introduction, various and diverse ventilation modes have found their way into clinical practice [1]. While older modes served rather simple goals, like reassuring adequate oxygenation and carbon dioxide elimination, newer modes target complex purposes like the prevention of ventilator–induced lung injury (VILI), continuous adaptation to constantly changing lung and patient conditions, weaning and even extubation readiness testing [2]. These so–called 'closed-loop' ventilation modes automatically adjust ventilator settings on the basis of physiologic signals and patient's activity while using advanced algorithms that prevent the use of potentially harmful ventilator settings.

One advanced and currently commercially available closed–loop mode is named INTELLiVENT–Adaptive Support Ventilation (INTELLiVENT–ASV) (Hamilton Medical, Bonaduz, Switzerland). INTELLiVENT–ASV automatically sets and adapts nearly all ventilator settings that are usually set, or adapted by the caregiver [3–7].

Wherever and whenever a closed-loop system supports caregivers with automated interventions, three aspects are of utmost importance – the 'effectiveness', the 'safety' and the 'efficacy'. In the context of invasive ventilation, 'effectiveness' concerns the ability to reach and maintain certain ventilatory and gas exchange targets, while preventing the use of ventilator settings that are considered potentially dangerous if not injurious, in invasively ventilated ICU patients. 'Safety' concerns aversions of intolerable derangements in gas exchange in these often critically ill patients. 'Efficacy' concerns issues like improved patient–ventilator synchrony and expeditious weaning from the ventilator. Ways to measure effectiveness, safety, and efficacy include physiologic parameters like ventilation parameters, gas exchange results, and various patient–centered outcomes, such as pulmonary complications, duration of ventilation, and length of stay in ICU or hospital, or even death [8].

In 2014, three Cochrane reviews concluded that closed–loop ventilation modes could not yet be seen as more effective, but at least as safe as conventional ventilation modes for use in ICU patients [9–11]. Consequently, caregivers remained uncertain if closed–loop ventilation modes should be part of their daily ICU practice [12–14], even when they have access to such closed–loop modes on

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Supplemental data for this article can be accessed here.

Article highlights

- VILI can be prevented by using a lower V_T, adequate levels of PEEP, and restrictive FiO_2;
- Effectiveness of a ventilation mode includes V_T, PEEP and FiO_2, and levels of dysoxemia;
- INTELLiVENT–ASV covers many parts of ventilation, from start of ventilation till extubation, in passive and active patients;
- INTELLiVENT–ASV is as effective as conventional ventilation in keeping V_T within lung–protective limits, and performs better than conventional ventilation with respect to time within predefined 'optimal' V_T zones;
- INTELLiVENT–ASV seems a safe mode of ventilation in critically ill patients;
- INTELLiVENT–ASV is as effective as conventional ventilation in avoiding dysoxemia; and
- Studies are highly needed to test whether INTELLiVENT–ASV is superior to conventional ventilation with respect to patient-centered outcomes.

their local ventilators. Evidence for benefit of closed–loop ventilation modes, in particular of INTELLiVENT–ASV, may have increased since then, as several studies have been performed after 2014. Following a comprehensive description of typical ventilator settings that are considered important in the prevention of VILI, and a more detailed description of the closed–loop ventilation mode of interest, we present the findings of a systematic review and meta–analysis regarding the effectiveness, efficacy and safety of INTELLiVENT–ASV.

2. Ventilator settings

Various ventilation settings play a key role in the prevention of VILI [15]. In patients with acute respiratory distress syndrome (ARDS), and also in patients with injured lungs, a lower tidal volume (V_T) should be considered, between 6 and 8 ml/kg predicted body weight (PBW) [16–19]. In patients without ARDS, a ventilation strategy targeting a low V_T (4–6 ml/kg PBW) may be as effective as one that targets an intermediate V_T (8–10 ml/kg PBW) [20]. The best level of positive end–expiratory pressure (PEEP) is much less certain [21], but aggressive use of higher PEEP with recruitment maneuvers has been shown to harm patients with ARDS [22]. In patients without ARDS, a lower PEEP strategy may be as efficient as a higher PEEP strategy [23]. There is increasing concern regarding a too liberal use of oxygen, or targeting too liberal oxygen levels, independent of whether a patient has ARDS or not [24,25].

Both driving pressure, the difference between the plateau pressure and PEEP, and mechanical power of ventilation, a mathematical approach that captures various ventilator settings including V_T, driving pressure, flow and respiratory rate, have an association with outcomes in patients with ARDS, as well as patients without ARDS [26–31]. While these two parameters certainly must be seen as biomarkers for existing lung injury, it could still be that simple adjustments of certain ventilator settings affect these parameters, possibly resulting in better outcomes. For instance, driving pressure could be reduced by using a lower V_T, respiratory rate could be kept low when accepting a certain level of hypercapnia, and PEEP could be used so that atelectasis is minimized while preventing overdistension.

Based on the above, for a ventilator mode to be effective and safe, the following is usually recommended:

- use an appropriate V_T (usually between 6 and 8 ml/kg PBW), certainly in ARDS but maybe also in patients without ARDS;
- titrate PEEP and fraction of inspired oxygen (FiO_2) by means of a lower PEEP/high FiO_2 table in patients with ARDS; this approach may also fit patients without ARDS
- target a lower driving pressure; and
- avoid both hyperoxia and hyperoxemia.

3. INTELLiVENT–ASV

INTELLiVENT–ASV is the successor of Adaptive Support Ventilation (ASV). With both ventilation modes, the clinician inputs patient's height and gender into the ventilator for an automatic calculation of PBW. Then, ASV provides ventilation based on an operator–set minute volume if a patient is passive, or on patient's demands when a patient is or becomes active. ASV uses the so–called Otis–equation to provide the best combination of V_T and RR to have the lowest work of breathing [32]. Adjustments are done on a breath–by–breath basis, and the ventilator switches from control ventilation to assisted ventilation, or *vice versa*, when the patient becomes active or when minute ventilation becomes too low, respectively. INTELLiVENT–ASV does the same, but also uses the so–called Mead–equation to adjust V_T, RR and PEEP to reach a low driving pressure [33,34]. Furthermore, with INTELLiVENT–ASV minute volume is constantly adjusted based on continuous end–tidal carbon dioxide ($etCO_2$) readings. Titrations of PEEP and FiO_2 are continuously adjusted based on continuous peripheral oxygen saturation (SpO_2) readings. For these last titrations, INTELLiVENT–ASV uses the so–called ARDS Network PEEP–FiO_2 tables [35,36]. The target ranges for $etCO_2$ and SpO_2 are set by the operator, in part by choosing a lung disorder (acute respiratory distress syndrome, and chronic obstructive pulmonary diseases) or a patient condition (brain injury), if present or applicable. INTELLiVENT–ASV facilitates weaning by gradually reducing minute volume and can be set to use spontaneous breathing trial by progressively reducing the ventilator settings within predefined limits, as such allowing timely identification of patients who are ready for extubation.

Thus, INTELLiVENT–ASV is able to cover nearly all parts of ventilation, from intubation and start of ventilation till extubation, and in both passive and active patients. Ventilator settings that are typically set and adjusted by the operator, like V_T and airway pressures, respiratory rate, and FiO_2, are with INTELLiVENT–ASV constantly adjusted in order to stay within predefined ranges decided by the user. It is important, though, that the user provides correct and meaningful input, like a correct body height (used by the ventilator to calculate the predicted body weight, used to determine and adjust V_T) and

a maximum airway pressure (used by ventilator to adjust airway pressures so to stay below it). In addition, the user can adjust the limits of each setting, and can even decide to turn off one or more of the algorithms used by INTELLiVENT–ASV.

4. Methods

4.1. Systematic review

A systematic search was performed in accordance with the 'Preferred Reporting Items for Systematic reviews and Meta Analyses' (PRISMA) recommendations [35]. The search was registered at PROSPERO with registration number CRD42016046842 [36]. For the purpose of this current report, we focus on the findings regarding INTELLiVENT–ASV.

4.2. Search strategy

In December 2018, initial searches were conducted in MEDLINE, EMBASE, the Cochrane Central register of Controlled Trials (CENTRAL), and Google Scholar. A final search was performed in November 2020. The search strategies were developed by two authors (ADB and EW) with the help of a medical librarian using the 'Cochrane Highly Sensitive Search Strategy' [37]. No restrictions were applied on publication date or language. Reference lists of studies identified by the searches and of previously published reviews were screened for studies that may have been missed by the original searches. To identify yet unpublished or ongoing studies, we also searched the databases of the NIH National Library of Medicine, the NHS International Standard Randomized Controlled Trial Number, and the trials registry of the WHO using typical terms like 'closed–loop ventilation', 'automated ventilation', and 'automated weaning'. Full search strategy for each database is presented in **Supplement e**Table 1.

4.3. Study selection

Three authors (ADBD, EW and MB) independently screened titles, abstracts and full texts for inclusion using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Parallel and crossover randomized clinical trials were selected for this systematic review and meta–analysis if the following criteria were met: (a) full–text publication available; (b) including only adult ICU patients; (c) comparing usual or standard care with INTELLiVENT–ASV; and (4) reporting effectiveness, efficacy and safety outcomes.

4.4. Extracted data

A form based on the data extraction format of the Cochrane Collaboration was used to extract the relevant data. Extracted information included 'study setting', 'study population', 'duration of the study,' 'details of the intervention', 'details of the control strategy', 'study methodology', and 'study outcomes', next to information for the assessment of the risk of bias. Data were extracted independently by three authors (ADB, EW, or MB). Disagreements were resolved by consensus. If no consensus was achieved, the opinion of a fourth independent reviewer (AB) was decisive. The corresponding author of an included study was contacted if the reported data considering study methods and results were incomplete or unclear.

4.5. Endpoints

For the purpose of this review, we used the following definitions for endpoints reflecting effectiveness, safety, and efficacy. We defined effectiveness endpoints as ventilator settings considered important for ventilation to be lung–protective, or reaching appropriate targets:

- V_T;
- PEEP;
- FiO_2;
- arterial pressure of carbon dioxide ($PaCO_2$);
- $etCO_2$;
- arterial oxygen saturation (SaO_2); and
- SpO_2.

We defined safety endpoints as:

- any reported inacceptable derangement in any ventilator parameters resulting in an immediate switch by the caregiver from INTELLiVENT–ASV to conventional ventilation;
- time spent within predefined ventilation ranges that could be seen as unsafe (when continuous data recording is available); and
- severe adverse events and adverse events related to the ventilation mode.

Efficacy endpoints were defined as outcomes frequently used in clinical studies of ventilation:

- mortality;
- length of stay in ICU;
- duration of ventilation;
- reintubation rate; and
- need for non–invasive ventilation after extubation.

4.6. Risk of bias and study quality

The Cochrane Collaboration's tool for assessing risk of bias was used by three authors (ADB, EW and MB) to independently assess the risk of bias for the included studies. The tool contains seven evidence–based domains including selection bias, performance bias, detection bias, attrition bias and reporting bias [38]. An independent fourth reviewer (AB) assisted to acquire consensus in case of disagreement.

4.7. Synthesis of results

Review Manager version 5.3 (RevMan 5.3, The Cochrane Collaboration) was used for the quantitative analysis [39], restricted to patient–centered outcomes. If outcomes were

judged to be sufficiently clinically homogenous, a quantitative synthesis was performed using random–effects models and 95% confidence intervals (95% CI). Risk ratios (RR) were used for dichotomous outcomes and mean differences (MD) were used for continuous outcomes. If the mean was not available, we used the median to estimate the mean as described before [40]. The sample size, median, and interquartile range were used to calculate an approximation of the standard deviation (SD) as described before [41]. Statistical heterogeneity was assessed with the I^2 test. Heterogeneity was considered as unimportant (0 to 40%), moderate (30 to 60%), substantial (50 to 90%), or considerable (75 to 100%) [37].

5. Results

5.1. Search results

The individual searches identified 2664 articles; 1172 articles were found in PubMed, 924 in MEDLINE, 50 articles in the Cochrane library, and 518 in Google Scholar. After removing duplicates, and screening for eligibility, 10 studies remained for the current analysis [42–51] (Figure 1).

The searches in trial registries identified 10 other studies; seven studies were completed but yet unpublished, three studies were still ongoing. Data of these 10 studies were not available for this review.

5.2. Study characteristics

Study characteristics are presented in Table 1. Of a total of 10 studies, six were parallel randomized trials [43,45–47,49,51], and four were randomized crossover trials [42,44,48,50].

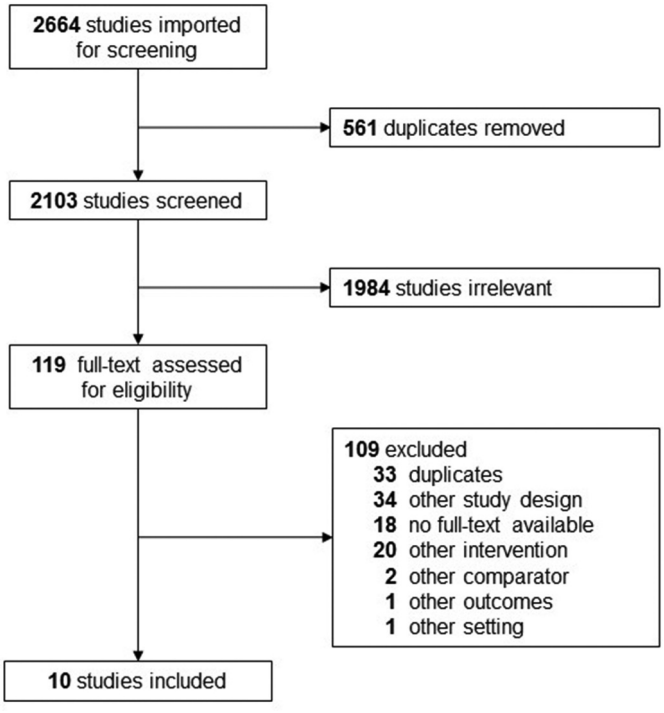

Figure 1. Search results.

INTELLiVENT–ASV was compared to its predecessor ASV in 2 studies [42,45], to pressure controlled or pressure support ventilation in five studies [44,46,48–50], and to volume-controlled ventilation or synchronized intermittent mandatory ventilation in 3 studies [43,47,51]. Four studies considered patients receiving postoperative ventilation in an ICU [43,45,47,51]; the other studies included mixed ICU populations including but not limited to patients with ARDS, patients with sepsis and patients with shock [42,44,46,49,50]. In one study, inclusion was restricted to patients with severe traumatic brain injury [48].

5.3. Risk of bias

Complete assessment of risk of bias per study is presented in Figure 2. Since blinding of personnel was not possible in the studies, due to the nature of the intervention, risk of performance bias was high in all studies. In five out of six parallel randomized trials, risk of selection bias was avoided through randomization with allocation concealment [43,46,47,49,51]. In the randomized crossover trials, risk of specific study design–related bias was low.

5.4. Effectiveness of INTELLiVENT–ASV (Table 2)

Eight studies reported on V_T [42–44,46,47,49–51]. Use of INTELLiVENT–ASV resulted in a lower V_T in three studies [42,43,51], a similar V_T in three studies [46,49,50], and higher V_T in one study [44]. INTELLiVENT–ASV was able to keep $V_T \leq$ 8 ml/kg PBW in four studies [43,46,49,51] and < 9 ml/kg PBW in two studies [42,44]. Only one study [50] reported a V_T of 10 ml/kg PBW in both groups. Median V_T with INTELLiVENT–ASV was < 8 ml/kg PBW in the ARDS patients [42]. In two studies, the percentage of time with V_T in a predefined 'optimal' range of between 6 and 10 ml/kg PBW, or ≤ 8 ml/kg PBW, was higher with INTELLiVENT–ASV [46,51].

Seven studies reported on PEEP and FiO_2 [42–44,46,49–51]. Use of INTELLiVENT–ASV resulted in higher PEEP in two studies [46,51], similar PEEP in four studies [43,44,49,50], and lower PEEP in one study [42]. Median PEEP was higher in patients with ARDS compared to patients without ARDS [42]. INTELLiVENT–ASV used a lower FiO_2 in three studies [42,43,51], but a similar FiO_2 in three other studies [44,46,49].

Eight studies reported on SpO_2 or SaO_2 [42–44,46,47,49–51]. With INTELLiVENT–ASV, oxygenation was similar in two studies [46,47], and lower in five studies [42–44,50,51]. SpO_2 and SaO_2 were <96% in three studies [42,46,50]. Hyperoxemia occurred less often with INTELLiVENT–ASV in two studies [43,49], and SpO_2 was more often in a predefined 'optimal' zone with INTELLiVENT–ASV in two studies [46,51].

Six studies reported on $PaCO_2$ [42–44,47,48,51], and seven on $etCO_2$ [43,44,46–49,51]. With INTELLiVENT–ASV, $PaCO_2$ was higher in three studies [42,43,51], and similar in three studies [44,47,48]. INTELLiVENT–ASV kept $PaCO_2$ within normal ranges in all studies. With INTELLiVENT–ASV, $etCO_2$ was similar to that with conventional ventilation in four studies [44,47–49], lower in one study [46], but higher in two other studies [43,51]. The percentage of time with $etCO_2$ in an 'optimal' or 'acceptable'

Table 1. Study Characteristics.

Authors	Ref	Design	N	Patients	Duration of the intervention	Control mode	Reported endpoints
Arnal *et al.* (2012)	42	randomized crossover trial	50	critically ill patients (38% normal lung, 62% ARDS)	4 hours (2 hours on each mode)	ASV	Effectiveness: V_T[a], PEEP, FiO_2, SaO_2[a], $PaCO_2$; Safety: premature interruptions
Lellouche *et al.* (2013)	43	randomized clinical trial	60	patients after cardiac surgery	4 hours	CMV/ PSV	Effectiveness: V_T[b], PEEP, FiO_2, SaO_2, $PaCO_2$, $etCO_2$[b]; Safety: premature interruptions, time within unsafe ventilation ranges; Efficacy: ICU mortality, reintubation rate, need for NIV, duration of weaning
Clavieras *et al.* (2013)	44	randomized crossover trial	14	critically ill patients (36% peritonitis, 29% pneumonia, 14% liver transplant)	48 hours (24 hours on each mode)	PSV	Effectiveness: V_T[a], PEEP[a], FiO_2[a], SpO_2, SaO_2, $PaCO_2$, $etCO_2$[a]; Safety: premature interruptions
Beijers *et al.* (2014)	45	randomized clinical trial	128	patients after cardiac surgery	Inclusion to extubation 0.14 ± 0.05 days[c]	ASV, PCV/PSV	Safety: premature interruptions; Efficacy: ICU mortality, hospital mortality, ICU length of stay, reintubation rate, need for NIV, duration of weaning
Bialais *et al.* (2016)	46	randomized clinical trial	80	patients after surgery (19%), critically ill patients (30% ARDS, 14% pneumonia, 11% sepsis)	48 hours	PAC/PSV	Effectiveness: V_T[a], PEEP[a], FiO_2[a], SpO_2[a], $etCO_2$[a]; Safety: premature interruptions, time within unsafe ventilation ranges; Efficacy: ICU mortality, hospital mortality, ICU length of stay, duration of ventilation
Fot *et al.* (2017)	47	randomized clinical trial	40	patients after cardiac surgery	Inclusion to extubation 0.13 [0.08–0.21] days[c]	SIMV + protocol. weaning	Effectiveness: V_T, $PaCO_2$, $etCO_2$; Safety: premature interruptions, time within unsafe ventilation ranges; Efficacy: ICU length of stay, reintubation rate, duration of weaning
Anan'ev *et al.* (2017)	48	randomized crossover trial	12	patients with severe isolated traumatic brain injury	24 h (12 h on each mode)	P-CMV	Effectiveness: $PaCO_2$, $etCO_2$
Arnal *et al.* (2018)	49	randomized clinical trial	60	critically ill patients (37% shock, 32% acute respiratory failure, 20% chronic respiratory failure exacerbation)	Inclusion to extubation/ death 6.0 [3.0–8.0] days[c]	VAC/PSV	Effectiveness: V_T, PEEP, FiO_2, SpO_2, $etCO_2$; Efficacy: ICU mortality, 28 days mortality, ICU length of stay, need for NIV, duration of ventilation, duration of weaning
Chelly *et al.* (2020)	50	randomized crossover trial	265	critically ill patients (52% acute respiratory failure, 25% coma, 7% cardiac arrest)	During DNP + 30 min before DNP per each mode	VCV/ BIPAP/PSV	Effectiveness: V_T, PEEP, SpO_2; Safety: SAEs (accidental extubation, bradycardia, cardiac arrest), premature interruptions, time within unsafe ventilation ranges
De Bie *et al.* (2020)	51	randomized clinical trial	220	patients after cardiac surgery	Inclusion to extubation 0.24 ± 0.17 days[c]	VCV/ PSV	Effectiveness: V_T[a], PEEP[a], FiO_2[a], SpO_2[a], $etCO_2$[a]; Safety: premature interruptions, time within unsafe ventilation ranges; Efficacy: ICU mortality, hospital mortality, ICU length of stay, reintubation rate, need for NIV, duration of ventilation, duration of weaning

[a] = ventilation parameter registered breath by breath; [b] = ventilation parameters continuously monitored by an operator; [c] = duration of ventilation in the INTELLiVENT–ASV group expressed by median [interquartile range] or mean ± standard deviation; ARDS = acute respiratory distress syndrome; DNP = daily nursing procedure; ASV = adaptive support ventilation; CMV = controlled mechanical ventilation; PSV = pressure support ventilation; PCV = pressure–controlled ventilation; PAC = pressure assist control; SIMV = synchronized intermittent mandatory ventilation; P–CMV = pressure-controlled mechanical ventilation; VAC = volume assist control; BIPAP = biphasic positive airway pressure; VCV = volume controlled ventilation; V_T = tidal volume; PEEP = positive end-expiratory pressure; FiO_2 = fraction of inspired oxygen; SaO_2 = arterial oxygen saturation; $PaCO_2$ = partial pressure of carbon dioxide; $etCO_2$ = end-tidal carbon dioxide; SpO_2 = peripheral oxygen saturation; SAEs = serious adverse events.

range was higher with INTELLiVENT–ASV in one study [51] and similar in another study [46].

5.5. Safety of INTELLiVENT–ASV

Five studies reported on the necessity to switch to conventional mode due to inacceptable derangement in any ventilation parameters [42–45,50]. INTELLiVENT–ASV did not affect this endpoint.

Five studies reported on time spent within predefined unsafe ventilation ranges [43,46,47,50,51]. The predefined ventilation parameter of interest and the ranges varied between studies and are reported in Table 3. No difference was observed between INTELLiVENT-ASV and conventional ventilation in two studies [46,47], with the exception of one ventilation parameter [46], while in three studies patients ventilated with INTELLiVENT-ASV spent less time within predefined unsafe ventilation ranges compared to conventional ventilation [43,50,51].

Only one study reported severe adverse events [50]. INTELLiVENT–ASV did not have more severe adverse events related to invasive ventilation compared to conventional ventilation.

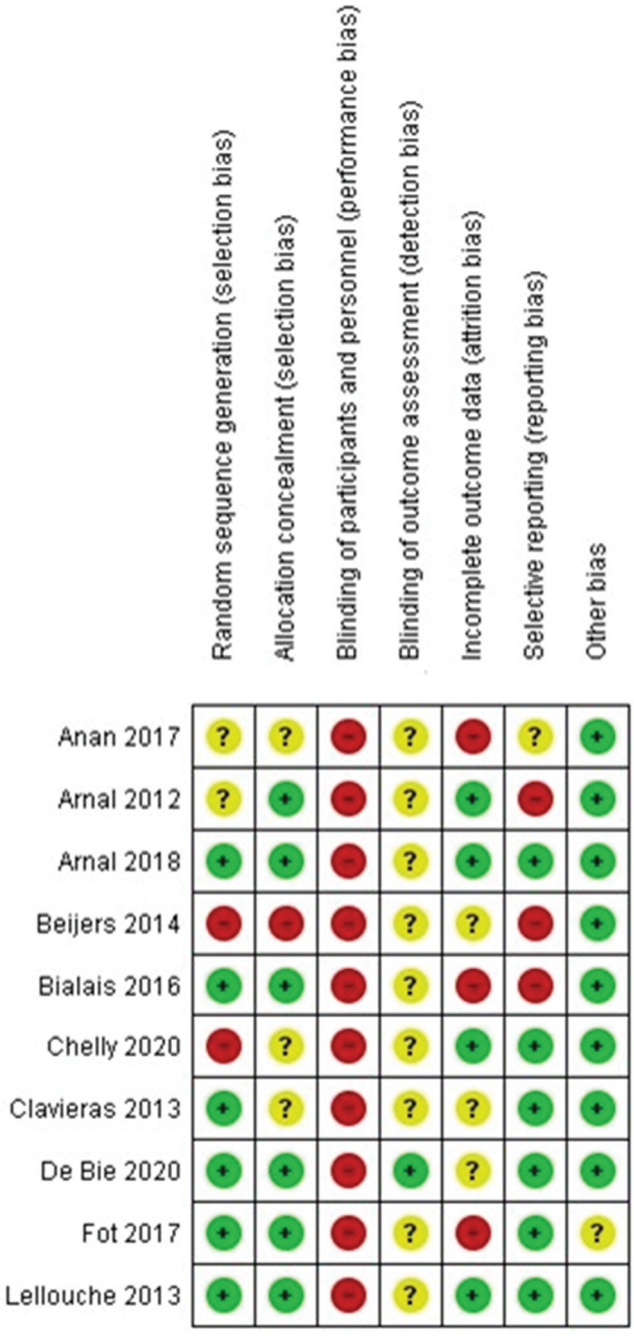

Figure 2. Assessment risk of bias.

5.6. Efficacy of INTELLiVENT–ASV (Table 4, Figures 3 and 4)

Four studies reported ICU mortality [43,46,49,51], one hospital mortality [46], one 28–day mortality [49], and one 30–day mortality [51]. Patients ventilated with INTELLiVENT–ASV had a lower hospital mortality in one study [46].

Three studies reported duration of invasive ventilation [46,49,51]. INTELLiVENT–ASV did not affect duration of ventilation, neither in the individual studies nor in the pooled analysis. Five studies reported duration of weaning [43,45,47,49,51]. INTELLiVENT–ASV did not affect duration of weaning, neither in the individual studies, nor in pooled analysis. Duration of stay in the ICU was not affected by INTELLiVENT–ASV, as was reported by five studies [45-47,49,51]. Four studies reported reintubation rates [43,45,47,51], and three studies reported use of NIV after extubation [43,45,51]. INTELLiVENT–ASV neither affected reintubation rates nor need for NIV after extubation.

6. Discussion

6.1. Summary of findings

The findings of this systematic review and meta–analysis including 10 randomized clinical trials can best be summarized as follows: 1) INTELLiVENT–ASV is at least as effective as conventional ventilation in keeping V_T low and in avoiding dysoxemia; 2) INTELLiVENT–ASV seems as safe as conventional ventilation; and 3) thus far, randomized clinical trials failed to show superiority of INTELLiVENT–ASV regarding efficacy.

6.2. Strengths of this systematic review

This review has several strengths. The systematic search was performed in accordance with the PRISMA recommendations, and was registered in PROSPERO. We used predefined endpoints, covering three important aspects – effectiveness, efficacy and safety. We reduced the risk of publication bias by not using any language restriction. The search for ongoing randomized clinical trial identified several additional studies, albeit that we could not use their data.

6.3. Effectiveness

V_T was lower, or at least similarly low with INTELLiVENT–ASV in six out of seven studies where median or mean V_T was reported, and almost always within the limits of what is called lung–protective. Only in one study V_T was 10 ml/kg PBW in both groups, which could probably have been due to pain and discomfort during mobilization. Of note, INTELLiVENT–ASV rapidly switches from control ventilation to assisted ventilation in case a patient becomes active. With assisted ventilation there is much less control over V_T, and since lung size can increase, usually V_T increases at similar pressures – consequently, V_T could increase with INTELLiVENT–ASV while pressures remain low. Interestingly, in studies that reported time during which V_T was within predefined 'optimal' zones, INTELLiVENT–ASV performed better than conventional ventilation.

With INTELLiVENT–ASV, SpO_2 or SaO_2 are lower or at least similar, often at a lower FiO_2 but with similar levels of PEEP. INTELLiVENT–ASV seems effective in preventing hyperoxemia by continuously aiming at the oxygenation target set by the physician, and thus reducing FiO_2 when the target has been reached. INTELLiVENT–ASV is programmed to use a lower PEEP/higher FiO_2 table when the oxygenation targets are not yet reached, but a higher PEEP/lower FiO_2 table when these targets have been reached. Consequently, INTELLiVENT–ASV tends to use higher PEEP. However, in the studies included in this review, PEEP was only higher in ARDS patients [42].

Table 2. Effectiveness of INTELLiVENT–ASV.

Author	Ref.	V_T, mL/Kg PBW	PEEP, cmH_2O	FiO_2, %	SpO_2/SaO_2, %	$PaCO_2/etCO_2$, mmHg
Arnal *et al.* (2012)	42	8.1 [7.7–8.6] vs 8.3 [7.8–9.0]**	8 [5–10] vs 10 [6–14]*	30 [30–39] vs 40 [30–50]**	96 [93–98] vs 97 [95–98] *[b]	37 [33–49] vs 37 [34–42]*[c]
Lellouche *et al.* (2013)	43	7.8 ± 0.5 vs 10.1 ± 1.3**	5 (5–10) vs 5 (5–8)	33 ± 6 vs 47 ± 10**	97 (93–99) vs 99 (92–99) **[b]	41 ± 4 vs 37 ± 4**[c] 38 ± 3 vs 33 ± 5**[d]
Clavieras *et al.* (2013)	44	8.4 [7.9–8.6] vs 7.6 [6.6–9.0]*	5.4 [5.0–7.8] vs 7.8 [5.0–9.7]	31 [30–32] vs 33 [30–41]	96 [95–97] vs 98 [97–99] *[a] 95 (92–99) vs 98 (95–99)*[b]	40.5 (36–44.5) vs 41.3 (37–48.5)[c] 37.8 [34.5–39.5] vs 38.5 [34.3–41.2][d]
Beijers *et al.* (2014)	45	-	-	-	-	-
Bialais *et al.* (2016)	46	7.9 [7.6–8.2] vs 7.5 [7.1–8.1]	7 [7–9] vs 6 [6–8]*	33 [34–42] vs 36 [33–44]	95 ± 2 vs 96 ± 2[a]	36 ± 7 vs 40 ± 8*[d]
Fot *et al.* (2017)	47	-	-	-	99 [97–99] vs 99 [97–100][a]	38 [37–42] vs 36 [32–40][c] 38 [35–40] vs 37 [32–38][d]
Anan'ev *et al.* (2017)	48	-	-	-	-	36 [35–37] vs 36 [34–38][c] 33 [32–37] vs 34.5 [31–39][d]
Arnal *et al.* (2018)	49	8.0 [7.0–8.1] vs 7.1 [7.0–9.0]	8 [5–11] vs 7 [5–9]	35 [32–42] vs 36 [32–44]	-	36 [34–40] vs 37 [33–43][d]
Chelly *et al.* (2020)	50	10 ± 2 vs 10 ± 3	9 ± 3 vs 9 ± 3	-	95 ± 3 vs 96 ± 3**[a]	-
De Bie *et al.* (2020)	51	6.4 (5.8–6.6) vs 7.8 (7.7–8) **	6.4 (5.6–6.6) vs 5.3 (5.2–5.4)**	33 (32–44) vs 43 (41–52)**	96.6 (96–97.2) vs 97.7 (97.5–98.1)**[a]	42 (37–42) vs 34.5 (34–35)**[d]

INTELLiVENT–ASV values are presented first; data are presented as mean ± standard deviation or median [interquartile range] or median (min–max); statistically significant differences are specified by * = p <0.05 and ** = p <0.01; [a] = SpO_2; [b] = SaO_2; [c] = $PaCO_2$; [d] = $etCO_2$; V_T = tidal volume; PEEP = positive end–expiratory pressure; FiO_2 = fraction of inspired oxygen; SpO_2 = peripheral oxygen saturation; SaO_2 = arterial oxygen saturation; $PaCO_2$ = partial pressure of carbon dioxide; $etCO_2$ = end–tidal carbon dioxide.

Table 3. Safety of INTELLiVENT–ASV.

Author	Ref.	Ventilation parameter	Not acceptable range	Time within not acceptable range (min)	Time within not acceptable range (%)	Incidence of episodes of derangements (n/%)
Lellouche *et al.* (2013)	43	V_T (ml/kg PBW)	> 12	1 ± 4 vs 15 ± 38*	0.5 vs 7.3*	-
		$etCO_2$ (mmHg)	< 25 or ≥ 51			
		Plateau pressure (cmH_20)	> 35			
		SpO_2 (%)	< 85			
Bialais *et al.* (2016)	46	V_T (ml/kg PBW)	< 3 or > 12[a,b,c]	-	1.3 (0.1–8.0) vs 0.8 (1.1–4.3)	-
		RR (breath/min)	< 10 or > 30[a] <10 or > 35[b,c]	-	0.9 (1.4–8.5) vs 1.7 (2.7–14.1)	-
		P_{max} (cmH_20)	> 30[a,b,c]	-	6.4 (13.3–31.6) vs 0.0 (7.1–30.4)**	-
		SpO_2 (%)	< 90[a,b] < 83[c]	-	0.5 (0.6–3.0) vs 0.7 (1.4–6.1)	-
		$etCO_2$ (mmHg)	> 55[a] < 26 or > 43[b] < 30 or > 65[c]	-	0.0 (0.1–2.3) vs 0.1 (1.6–15.8)	-
Fot *et al.* (2017)	47	V_T (ml/kg PBW)	< 6	-	-	3/17 vs 11/55
			> 10	-	-	1/6 vs 5/25
		$etCO_2$ (mmHg)	< 25	-	-	5/28 vs 7/35
			> 45	-	-	6/33 vs 9/45
		RR (breath/min)	> 30	-	-	3/17 vs 7/35
		SpO_2 (%)	< 90	-	-	0 vs 2/10
Chelly *et al.* (2020)	50	SpO_2 (%)	< 90	5 ± 12 vs 6 ± 11*	-	30/11 vs 50/19*
			< 85	2 ± 6 vs 3 ± 8*	-	69/26 vs 92/35*
De Bie *et al.* (2020)	51	V_T (ml/kg PBW)	> 12	-	1.5 ± 4.7 vs 3.6 ± 8.1*	23,710/4.7 vs 38,929/7.3**[d]
		P_{max} (cmH_20)	≥ 36			
		$etCO_2$ (mmHg)	< 25 or ≥ 51			
		SpO_2 (%)	< 85			

INTELLiVENT–ASV values are presented first; data are presented as mean ± standard deviation or median (95% confidence interval for the mean); statistically significant differences are specified by * = p <0.05 and ** = p <0.01; V_T = tidal volume; $etCO_2$ = end–tidal carbon dioxide; SpO_2 = peripheral oxygen saturation; RR = respiratory rate; P_{max} = maximum airway pressure; [a] = normal lungs/ARDS; [b] = brain injury; [c] = chronic hypercapnia; [d] = number of breaths.

INTELLiVENT–ASV adjusts V_T, RR and PEEP to reach a lower driving pressure. Driving pressure was frequently not reported in the reviewed studies. Future studies can focus on, or at least report this parameter.

6.4. Safety

The variability in definitions of unsafe ventilation ranges makes a synthesis of the results regarding safety challenging. INTELLiVENT–ASV seems at least as safe as conventional ventilation in all studies. However, in one study [46] P_{max} was more often in the unsafe range with INTELLiVENT–ASV than with conventional ventilation, but no statistical difference was observed in the mean P_{max} between the two groups. Although this was not confirmed by a more recent study on post–cardiac surgery patients [51], it requires further attention in future studies.

Table 4. Efficacy of INTELLiVENT–ASV.

Author	Ref.	ICU mortality (%)	Hospital/28–day/30–day mortality (%)	ICU length of stay (days)	Reintubation rate (%)	Need for NIV (%)	Duration of ventilation (days)	Duration of weaning (days)
Arnal *et al.* (2012)	42	-	-	-	-	-	-	-
Lellouche *et al.* (2013)	43	0 vs 0	-	-	0 vs 0	0 vs 0	-	0.22 [0.18–0.31] vs 0.28 [0.2–0.36]
Clavieras *et al.* (2013)	44	-	-	-	-	-	-	-
Beijers *et al.* (2014)	45	1 vs 0	1 vs 0	0.14 [0.1–0.16] vs 0.13 [0.09–0.17]	0 vs 0	0 vs 0	-	0.14 ± 0.05 vs 0.15 ± 0.12
Bialais *et al.* (2016)	46	21 vs 29	3 vs 18*[a]	11.5 [10.8–20.8] vs 13.0 [11.6–24.3]	-	-	5.5 [6.0–13.0] vs 8.0 [6.5–15.3]	-
Fot *et al.* (2017)	47	-	-	2 [1.0–3.0] vs 1 [1.0–3.0]	0 vs 0	-	-	3.2 [1.9–5.2] vs 3.3 [2.6–4.2]
Anan'ev *et al.* (2017)	48	-	-	-	-	-	-	-
Arnal *et al.* (2018)	49	30 vs 23	30 vs 23[b]	10.0 [6.0–13.0] vs 9.0 [5.0–14.0]	-	-	6.0 [3.0–9.0] vs 6.5 [4.0–14.5]	4.0 [1.0–5.5] vs 2.0 [1.0–4.0]
Chelly *et al.* (2020)	50	-	-	-	-	-	-	-
De Bie *et al.* (2020)	51	2.8 vs 0	2.8 vs 0[c]	0.3 [0.3–0.6] vs 0.4 [0.3–0.7]	1.9 vs 1.9	1.9 vs 7.2	0.2 [0.14–0.3] vs 0.21 [0.14–0.33]	0.11 [0.04–0.09] vs 0.11 [0.05–0.23]

INTELLiVENT-ASV values are presented first; data are presented as mean ± standard deviation or median [interquartile range] or median (95% confidence interval for the mean); statistically significant differences are specified by * = p <0.05 and ** = p <0.01; [a] = hospital mortality; [b] = 28–day mortality; [c] = 30–day mortality; ICU = intensive care unit; NIV = non–invasive ventilation.

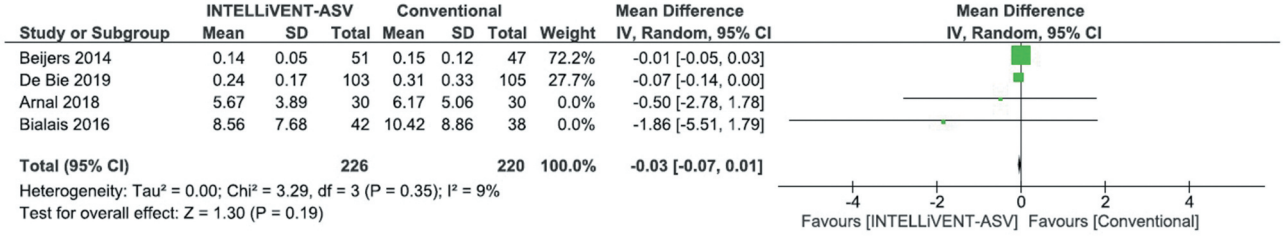

Figure 3. Forest plot of duration of mechanical ventilation.

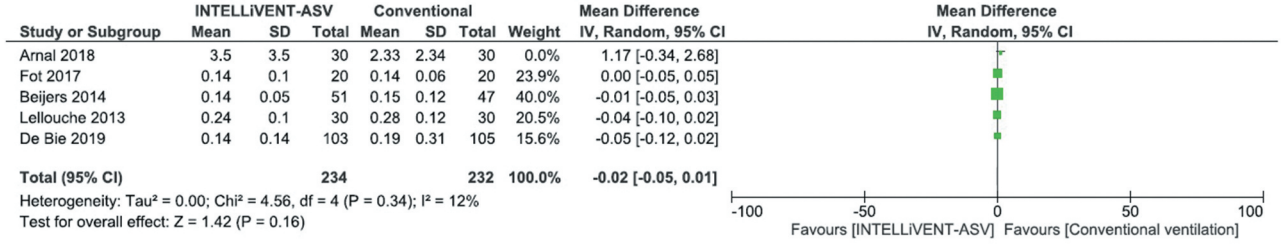

Figure 4. Forest plot of duration of weaning.

Once INTELLiVENT–ASV has reached the oxygenation target, the algorithm follows the higher PEEP/lower FiO_2 table with the purpose of avoiding alveolar de–recruitment. It is questionable if this approach is beneficial for all patients as, thus far, randomized clinical trials failed to show clinical benefit of a higher PEEP over a lower PEEP strategy [52–54], and one study even showed harm of using a higher PEEP strategy in patients with ARDS [22]. Of note, INTELLiVENT–ASV allows the clinician to decide the maximum level of PEEP that can be used by setting an upper limit for this parameter.

6.5. Efficacy

Thus far, most studies of INTELLiVENT–ASV have been too small to allow firm conclusions regarding the efficacy of INTELLiVENT–ASV. Also, studies used various populations,

ranging from critically ill patients with ARDS who need complex ventilation that is usually needed for days, to patients receiving simple postoperative ventilation that is usually applied for only hours. Also, the outcomes used varied substantially between the studies.

Sufficiently sized studies are highly needed. As of late 2020, we are aware of at least two sufficiently sized randomized clinical trials, i.e., 'EASiVENT' (NCT04400643), a multicenter international study in the US, France and Switzerland, with the objective of evaluating the efficacy and safety of INTELLiVENT–ASV in an adult ICU population, and 'ACTiVE' (NCT04593810), a multicenter international study in the Netherlands and Italy, with the objective to compare the number of ventilator–free days and alive at day 28 and the quality of breathing between INTELLiVENT–ASV and conventional ventilation. Of note, INTELLiVENT–ASV is commercially available in many countries, but, for example, not yet in the United States of America.

6.6. Limitations of this systematic review

This review has limitations. First, besides randomized clinical trials, it included four crossover trials, lowering the level of evidence. However, crossover designs also have the advantage of eliminating between–participant variations. As these studies did evaluate safety and effectiveness, we would have missed important information if we had excluded them from this review. Second, though other automated modes are currently available for use in critically ill patients, we restricted the analysis to INTELLiVENT–ASV in order to get homogeneity of the studied intervention and because INTELLiVENT–ASV is currently the most advanced and complete mode of ventilation – indeed, in contrast to other automated modes, INTELLiVENT–ASV works under all conditions, i.e., not only during the weaning phase when a patient becomes active, but also in passive patients. Third, we restricted this review to studies in adult patients, and none of the studies reported on 'special' conditions or situations, like one–lung ventilation, or ventilation in transplant patients. Fourth, we did not report other outcomes that could also be affected by INTELLiVENT–ASV, like duration of spontaneous breathing, and patient–ventilator asynchronies, due to lack of studies on these topics. Fifth, heterogeneity in studied cohorts and duration of the intervention hampers generalizability. Last but not least, one major limitation of all included studies was the impossibility of blinding patients and personnel due to the nature of the intervention. This leads to high risk of performance bias and the Hawthorne effect, which usually cannot be avoided in studies of ventilation in critically ill patients.

7. Conclusion

In conclusion, INTELLiVENT–ASV is an effective and safe fully closed–loop ventilation mode with regard to V_T and oxygenation titrations, but thus far the randomized clinical trials failed to show superiority in respect of efficacy. Future studies are needed to test the effects of INTELLiVENT–ASV on patient–centered endpoints.

8. Expert opinion

In this review, we brought together the available evidence for effectiveness, safety and efficacy of INTELLiVENT–ASV. The effectiveness and safety of this automated mode of ventilation are at least comparable to conventional ventilation; the randomized clinical trials reported thus far, however, failed to show superiority in respect of efficacy. The actual search adds to the literature as it focuses exclusively on one automated mode of invasive ventilation and by selecting high-quality studies.

Randomized clinical trials of INTELLiVENT–ASV, using clinically relevant patient-centered outcomes, are currently being performed. These and other studies will show whether or not INTELLiVENT–ASV has the potential to improve outcomes of critically ill patients, i.e., duration of mechanical ventilation and duration of weaning. A reduction in duration of ventilation, on its part, could affect multiple secondary clinical endpoints, such as length of ICU and hospital stay, ICU–acquired weakness and mechanical ventilation complications, e.g., ventilator–associated pneumonia or barotrauma. Moreover, a reduction in duration of ventilation could also affect economical endpoints, making this mode of ventilation relevant for daily practice, both from a patient and a healthcare–efficiency perspective.

Future studies could also address the impact of INTELLiVENT–ASV on other important ventilation subjects in both ARDS and non–ARDS patients, i.e., mechanical power and driving pressure, which together reflect the 'intensity of ventilation', and patient–ventilator asynchronies.

Several studies of INTELLiVENT–ASV showed a reduction in required interactions with the ventilator, meaning that use of INTELLiVENT–ASV could reduce workload. While especially of interest during the current coronavirus disease 2019 pandemic during which many patients need ventilatory support, any reduction in workload of ICU doctors and nurses should be embraced at all times, as many studies have shown a correlation between workload and ICU mortality.

Utilizing automated modes of ventilation, like INTELLiVENT–ASV, requires healthcare workers to provide correct inputs, to set target ranges for SpO_2 and $etCO_2$, and to leave settings that are usually set by healthcare workers to the ventilator. This is very different from how non–automated modes are used. This change in interaction can be a real challenge for healthcare workers. Not surprisingly, therefore, automated modes like INTELLiVENT–ASV could cause resistance from experienced healthcare workers. In a highly–controlled environment like an ICU, it could be difficult to 'entrust' a delicate process like lung–protective ventilation to a set of algorithms within a ventilator, a phenomenon also known as the 'black box effect'. This aspect of automated ventilation can be a bigger obstacle to its implementation than trusting that it could be as safe and effective as non–automated ventilation.

It should be noted that algorithms used in automated modes of ventilation can and must change with the appearance of evidence for benefit or harm of certain settings – for instance, it is highly uncertain whether the use of a higher PEEP level really yields clinical benefit. If this is not the case,

the algorithms should be changed so that the use of a higher PEEP is prevented. In other words, updates are required – with every new piece of evidence coming in.

Abbreviations

ARDS: acute respiratory distress syndrome
ASV: Adaptive Support Ventilation
ICU: intensive care unit
$etCO_2$: end-tidal carbon dioxide
FiO_2: fraction of inspired oxygen
MD: mean differences
PBW: predicted body weight
PEEP: positive end-expiratory pressure
PRISMA: Preferred Reporting Items for Systematic reviews and Meta Analyses
RR: Risk ratios
SaO_2: arterial oxygen saturation
SpO_2: pulse oximetry saturation
V_T: tidal volume
VILI: ventilator–induced lung injury

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